Age-Structured Epidemic Models with Heterogeneous Mixing

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March 9, 2006

Abstract

The spread of a disease is sensitive to the mixing patterns present in the affected population and to the precautions that the population takes to reduce the transmission of the disease. We investigate the impact that different mixing assumptions have on the spread of smallpox in a age-structured differential equation model. We use a normally mixing population and a population that reduces its number of contacts in response to knowledge of a smallpox outbreak to compare the effect the population mixing pattern has on an epidemic. We also consider the impact of heterogeneity in susceptibility (partial immunity) and infectivity within the population on the spread of an epidemic. We identify a basic reproduction number $\Re_0$ and based on this threshold parameter we show how much people have to change their behavior in order for the disease to die out. Different mixing patterns lead to differences in disease prevalence, cumulative number of new

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infections and final epidemic size. Furthermore, we develop examples which show that heterogeneous mixing can lead to more severe epidemics. Our analysis demonstrates that the combination of residual immunity, realistic mixing patterns and behavioral changes during an outbreak can play a key role in halting an epidemic such as smallpox.

Key Words: Mixing patterns, infectious diseases, smallpox, mathematical models, random mixing, EpiSims, behavioral change, epidemic models.

1 Introduction

Mathematical models of the transmission of infectious agents can be useful tools in understanding patterns of disease spread and assessing the effects of different interventions. The spread of infectious diseases depends upon the contact patterns in the population. Contact patterns guide in identifying people with high risk of contracting an infection and where the outbreak could be effectively intercepted. We investigate how to account for the contact patterns in an epidemic model to better understand disease spread.

Any realistic model for the spread of an infectious disease must take into account the mechanism of its transmission, the pattern of mixing among the population, the susceptibility within the population, the virulence of the infection, the probability of transmission per contact, and the changes in behavior in the affected population in response to an epidemic. Several mathematical models have studied the effects of different mixing patterns [4, 23, 25, 27, 28, 31, 32] using mixing functions or mixing matrices defined in compartmental models and networks models [52]. Techniques have been developed to incorporate non-random mixing into epidemic models, including restricted mixing [29], proportional mixing [19, 42], preferred mixing [20, 42], selective mixing [33], and non-proportionate mixing [1]. Network epidemic models have been used to investigate sequential partnership patterns [34], concurrency in relationships [34], the impact of various social biases on the spread of epidemics [13, 45], and other topics related to mixing [35]. Network and compartmental epidemic models have been used to model several infectious diseases; however, very few models have incorporated the impact of realistic mixing patterns in the presence of population heterogeneity.

The assumption of a homogeneously mixing population is often sufficient to obtain general insights. However, it can lead to an overestimation of the final epidemic size and the magnitude of the interventions needed to stop an epidemic. Heterogeneity within the population, such as age-dependent susceptibility, can also contribute to overestimating the interventions needed when designing public health policy. For example, smallpox was eradicated worldwide in the

1970s. Because the vaccine itself carries potential health risks, the United States discontinued smallpox vaccinations in 1972 [6]. Therefore, more than half of the US population has received the smallpox vaccine, and recent studies have shown that some of these individuals may still have partial protection against smallpox [2, 10]. This protection should greatly reduce the number of severe and fatal cases of disease expected in a bioterrorist attack. Therefore, there are clear age-dependent differences in susceptibility that must be taken into account when developing models that will guide public health policy during a smallpox attack.

Age-dependent risks and residual protection have been mostly neglected in the mathematical models proposed to guide response strategies for a smallpox outbreak [5, 11, 30, 36, 39]. Only some mathematical models for the dynamics of smallpox have incorporated the effects of residual immunity. Halloran et al. [18] used a stochastic simulation of smallpox in a community of 2000 people in their efforts to compare mass vaccination versus ring vaccination under different scenarios. They concluded that ring vaccination would be more competitive in the presence of preexisting immunity. However, they divided the population into two classes (with and without residual immunity) and did not consider age-dependent risks, heterogeneous mixing and behavioral changes. Nishiura et al. [41] used a deterministic model in a population of 1 million people to study the impact of long-lasting vaccine-induced immunity. They divided the population into three classes (never vaccinated, one vaccination, two vaccinations), also assumed homogeneous mixing and did not incorporate age-dependent risks and behavioral changes. They observed that an epidemic could be greatly affected by the residual immunity within the population and that vaccination should be given in accordance to immunity level.

Responses to an infectious disease in a community can reduce morbidity and mortality; for example, significant changes in behavior among men who have sex with men have been credited with decreases in prevalence of HIV/AIDS and other sexually transmitted diseases [17, 20, 24, 51]. Recent experiences with the SARS epidemics show that an outbreak of a deadly disease like smallpox would generate dramatic behavioral changes [8, 37, 43]. Del Valle et al. [48] used a deterministic model to study the effects of behavioral changes during a smallpox outbreak. They demonstrated that behavioral changes can have a dramatic impact in slowing an epidemic and reducing the total number of cases. However, they used homogeneous mixing and differences in susceptibility based on age were not incorporated

Age structure in epidemic models has been considered by many authors, because of the recognition that transmission dynamics of certain diseases cannot be correctly described by the traditional epidemic models with no age dependence. The age incidence of smallpox depends mainly on the acquired immunity of the exposed population due to vaccination and on the age-dependent risks present in the population. Therefore, we develop an age structured model

for the disease transmission dynamics of smallpox in a population that is subjected to residual immunity and age-dependent risks. We assume that the population is closed (no immigration and births are considered) and that there is only one disease in operation. Furthermore, we use different mixing matrices (normal, reduced, random, and segregated) and compare their effect on the final epidemic size of a smallpox outbreak.

Our results show that different mixing assumptions lead to differences in the disease prevalence, the cumulative number of new infections and the final epidemic size. Normal, reduced and segregated mixing lead to smaller final epidemic sizes and larger susceptible population when compared to random mixing. Nevertheless, normal mixing can lead to epidemics that are more severe than segregated mixing. One implication of this result is that heterogeneous mixing plays an important role in the transmission of the disease. Therefore, in the face of an epidemic, the population not only has to reduce their number of contacts, but they have to reduce their mixing patterns.

Furthermore, our simulations show that when residual immunity is considered, the final epidemic size is reduced for all mixing assumptions. We also observe that the age groups with high susceptibility are less affected by the disease than those with less susceptibility. Therefore, one implication of this result is that if vaccination of smallpox becomes necessary, the smallpox vaccine should be given according to the immunity present in the population.

We also identified the epidemic threshold parameter $\Re_0$ and show that $\Re_0$ is proportional to the daily average number of contacts per person. Therefore, based on this finding we can estimate how much people have to reduce their contacts in order for the epidemic to die out. This result can guide public health officials in persuading the population to change their behavior by reducing their number of contacts depending on the value of $\Re_0$.

The paper is structured as follows. After introducing the discrete age structured model, we derive an expression for the basic reproduction number. Next, we introduce the different mixing matrices and estimate the model parameters. The simulations and the sensitivity analyses illustrate the relative importance of different mixing parameters and behavioral changes on the epidemic predictions. Finally, the epidemiological implications of these mixing matrices are discussed.

2 The Mathematical Model

We formulate the transmission dynamics model for a single outbreak of smallpox in a heterogeneously mixing population. We divide the population into three main epidemiological classes, susceptible (S), infected (I) and recovered (R) [26]. These classes are further divided into

age groups with heterogeneous mixing and different susceptibilities and infectiousness base on age and residual immunity from previous smallpox vaccinations. This allows us to take into account the differences in infectivity for diseases such as smallpox, i.e. latent or incubation period, prodromal period and symptomatic or infectious period. We will apply the model to a smallpox outbreak, and assume that the course of the outbreak is short compared with the life of an individual, therefore, births, aging and natural deaths are not included.

For our multi-group SIR model with staged progression [26, 40], we consider 91 age groups ($n = 91$) with 1-year intervals: 1, 2, 3, $\cdots$, 88, 89, 91 and 3 infection stages (m=3; exposed, prodromic and infectious). Using the transfer diagram in Figure 1, we arrive at the following nonlinear system of differential equations:

$$\begin{aligned}
\frac{dS_i}{dt} &= -\lambda_i(t)S_i(t), \quad \text{for } 1 \le i \le n \\
\frac{dI_{i1}}{dt} &= \lambda_i(t)S_i(t) - (\omega_{i1} + \mu_{i1})I_{i1}(t), \\
\frac{dI_{ik}}{dt} &= \omega_{i,k-1}I_{i,k-1}(t) - (\omega_{ik} + \mu_{ik})I_{ik}(t), \quad \text{for } 2 \le k \le m \\
\frac{dR_i}{dt} &= \omega_{im}I_{im}
\end{aligned} \tag{1}$$

where $\lambda_i(t)$ is the force of infection (defined later); ω_{ik} is the relative rate of disease progression for a person in age group i and infection stage k; and μ_{ik} is the disease-induced relative death rate for age group i in infectious stage k.

We define λ_i as the relative rate at which the susceptible population in age group i gets infected and progresses to stage I_{i1}. We calculate this as the sum of the rate of disease transmission from each infected subgroup, I_{ik}, to the susceptible group, S_i. This means that a susceptible person in group i can get infected by an infected person in any group or infection stage. That is,

$$\lambda_i(t) = \sum_{j=1}^{91}\sum_{k=1}^{3}\lambda_{ijk}(t). \tag{2}$$

Here, λ_{ijk} is the rate of disease transmission from the infected people I_{jk} in stage k of age group j to the susceptibles in S_i in age group i. We define λ_{ijk} in (2) as the product of the number of contacts per unit time that each individual in age group i has with age group j; the probability of disease transmission per contact between an infected in group j and a susceptible in group i (which is the product of the susceptibility α_i of someone in S_i, the infectivity ξ_{jk} and the probability of transmission P_{ij} based on the average duration of contacts between age groups i

and j); and the fraction of contacts that are infected. That is,

$$\lambda_{\mathbf{ijk}} = \begin{pmatrix} \text{Number of} \\ \text{Contacts per} \\ \text{Unit Time} \end{pmatrix} \begin{pmatrix} \text{Probability of} \\ \text{Disease Transmission} \\ \text{per Unit Time} \end{pmatrix} \begin{pmatrix} \text{Fraction of} \\ \text{Contacts that} \\ \text{are Infected} \end{pmatrix},$$

$$\lambda_{\mathbf{ijk}} = \quad (\gamma_{ij}(t)) \quad (\alpha_i \xi_{jk} P_{ij}) \quad \left(\frac{I_{jk}(t)}{N_j(t)}\right) \quad , \tag{3}$$

the numerator of $(I_{jk}(t)/N_j)$ gives the fraction of individuals of age j who are in infected stage k, and the denominator, $N_j(t)$, is the total population size in age group j. That is

$$N_j(t) = S_j(t) + \sum_{k=1}^{m} I_{jk}(t) + R_j(t). \tag{4}$$

Summing over all the infection stages gives the force of infection from all infecteds to the susceptibles in group i. Multiplying this quantity by the number of susceptibles in age group i as in (1) gives the rate of change of new infecteds.

2.1 Definition of the mixing

The pattern of contacts between different age groups plays an essential role in determining the spread of disease. We assume people in each age group behave the same way when selecting a contact, but have biases between age groups. In other words, mixing within each age group is assumed to be homogeneous but there is heterogeneous mixing among the age groups. This mixing between age groups is one of the most important factors in modeling diseases. The mixing depends on the desirability of an active individual, the acceptability of his/her potential contacts, and the availability of these potential contacts.

Let d_{ij} be the desirability of people in age group i to have a contact from age group j; that is, d_{ij} is the fraction of people in age group j with whom an individual in age group i desires forming a contact. Thus d_{ij} describes the desirability of people in age group i to have a contact from age group j and the acceptability of people in age group j to people in age group i.

Under the condition that enough potential contacts are available, the probability ρ_{ij} that a contact forms between individuals from age group i and age group j, is the product of the availability of age group i for age group j, d_{ji}, and the desirability of age group i for age group j, d_{ij}. Note that we can also alternatively define ρ_{ij} as the preference for a contact between age group i and age group j. With this alternative definition, the ρ_{ij}'s are no longer restricted to being less than or equal to 1.

We define a_i to be the preferred number of social contacts per unit time for a person in age group i. The probability that a contact is with a person from age group j is $a_j N_j/(\sum_l a_l N_l)$ where N_j is the total population size of age group j defined in (4). This also characterizes the availability of contacts in age group j. Hence, the probability of a contact forming between individuals from age group i and age group j is $\rho_{ij} a_j N_j/(\sum_l a_l N_l)$ (again, if we think of ρ_{ij} as a preference then this now becomes a preference of forming contacts.)

The desirability matrix need not be symmetric (i.e. $d_{ij} \neq d_{ji}$, when $i \neq j$), but the probability of a contact forming is symmetric since $\rho_{ij} = d_{ij} d_{ji}$ implies $\rho_{ij} = \rho_{ji}$. Also, we note that there is no constraint on $\sum_j d_{ij}$, which may be less than or greater than one.

Two special cases of the model (1) with the infection rate, (2) and (3), are the restricted mixing model when $d_{ij} = 0$ (hence $\rho_{ij} = 0$, $i \neq j$) and the proportional mixing model when $d_{ij} = 1$, for $\{i, j\} = 1, \cdots, n$.

We denote the number of contacts per unit time of people in age group i with people in age group j by C_{ij}. The number of contacts with people in age group i that people in age group j have is also C_{ij}, that is $C_{ij} = C_{ji}$. These are the balance constraints that need to be satisfied at all times. In multi-group models where an attempt is made to directly control the number of contacts formed between age groups, these balance conditions usually are artificially enforced. However, in the selective mixing model, the balance constraint

$$C_{ij} = \rho_{ij} \frac{a_j N_j}{\sum_l a_l N_l} a_i N_i = \rho_{ji} \frac{a_i N_i}{\sum_l a_l N_l} a_j N_j = C_{ji} \tag{5}$$

is automatically satisfied. Thus, by using the acceptability d_{ij} or desirability d_{ji} of an individual from age group i to an individual from age group j as the primary control variable in these models (instead of the number of contacts an individual from age group i desires from age group j), the balance constraints become a natural consequence of the model, rather than an artificially imposed constraint.

The number of contacts per individual per unit time in many multi-group models is assumed to be constant. When all d_{ij}'s equal one (proportional mixing), this is also true for the selective mixing model. However, if the mixing is biased, the actual number of contacts, denoted by γ_i, for the selective mixing model will vary in time depending on the combination of desirability, acceptability, and availability.

Define $\tilde{P}(i)$ as the probability that an individual in age group i finds a contact from any age group. The actual number of contacts per person in age group i,

$$\gamma_i = a_i \tilde{P}(i) = a_i \left(\sum_{j=1}^{n} \rho_{ij} \frac{a_j N_j}{\sum_l a_l N_l} \right), \tag{6}$$

reaches its maximum a_i only for the proportional mixing, where $\rho_{ij} \equiv 1$ (i.e. everyone is acceptable as a contact). Therefore, the average number of contacts per person (6) is the sum over the contacts with each age group, that is,

$$\gamma_{ij}(t) = a_i \rho_{ij} \frac{a_j N_j(t)}{\sum_{l=1}^{n} c_l N_l(t)} \qquad \text{with} \qquad \rho_{ij} = d_{ij} d_{ji}. \tag{7}$$

If the mixing is biased, the acceptability and the availability of contacts must be taken into consideration and a limitation may occur. Then $\rho_{ij} \leq 1$, and hence $\gamma_i \leq a_i$. However, we think of the ρ_{ij}'s as preferences, then it is possible for the actual number of contacts per person, γ_i, to be greater than the preferred number of contacts, a_i.

3 The Basic Reproduction Number, $\Re_0$

The biological meaning of the basic reproduction number is the average number of secondary cases produced by one infected individual during the infected individual's entire infectious period. In an epidemic model the magnitude of $\Re_0$ determines whether or not an epidemic occurs. Typically, the disease dies out if $\Re_0 < 1$, whereas if $\Re_0 > 1$ the disease persists in the population. In a simple SIR model, let γ be the average number of contacts per unit time per individual, β be the probability of transmitting the infection per contact, τ be the mean duration of the infection period, and S_0/N_0 be the initial susceptible fraction. In this model, the basic reproduction number is given by the following intuitive formula:

$$\Re_0 = \gamma \beta \tau \frac{S_0}{N_0}. \tag{8}$$

This formula gives insight into the transmission dynamics of infectious diseases for this very simple epidemiological model.

The "next-generation operator" approach [50] can be used to find an expression for the basic reproduction number $\Re_0$ for our epidemic model. The computation is done by linearizing system (1) around the disease-free steady state and by identification of conditions that guarantee growth in the infected classes. The disease-free steady state has I_{11}, I_{12}, I_{13}, I_{21}, I_{22}, I_{23}, $\cdots$, $I_{91,1}$, $I_{91,2}$, $I_{91,3}$ equal to zero with initial susceptible sizes S_i^0 positive. The resulting 273 dimensional linearized system is of the form $\dot{\mathbf{X}} = (\mathbf{F} - \mathbf{V})\,\mathbf{X}$, where

$$\mathbf{X} = \begin{bmatrix} I_{11} & I_{12} & I_{13} & \cdots & I_{91,1} & I_{91,2} & I_{91,3} \end{bmatrix}^T,$$

The $\mathbf{F}$ matrix has nonzero entries in every column of rows 1, 4, 7, etc. and all zeros in rows 2, 3, 5, 6, 8, 9, etc. The entries in the 3 columns $3(j-1)+1$, 2, 3 of row $1+3(i-1)$ are

$$\frac{\gamma_{ij}\alpha_i \xi_{j1} P_{ij}}{N_j^0}, \frac{\gamma_{ij}\alpha_i \xi_{j2} P_{ij}}{N_j^0}, \frac{\gamma_{ij}\alpha_i \xi_{j3} P_{ij}}{N_j^0}.$$

The $\mathbf{V}$ matrix is block diagonal with 3x3 blocks of the form

$$B = \begin{bmatrix} \omega_{j1}+\mu_{j1} & 0 & 0 \\ -\omega_{j1} & \omega_{j2}+\mu_{j2} & 0 \\ 0 & -\omega_{j2} & \omega_{j3}+\mu_{j3} \end{bmatrix},$$

which has an inverse of the form

$$B^{-1} = \begin{bmatrix} \frac{1}{\omega_{k1}+\mu_{k1}} & 0 & 0 \\ \frac{\omega_{k1}}{\omega_{k1}+\mu_{k1}}\frac{1}{\omega_{k2}+\mu_{k2}} & \frac{1}{\omega_{k2}+\mu_{k2}} & 0 \\ \frac{\omega_{k1}}{\omega_{k1}+\mu_{k1}}\frac{\omega_{k2}}{\omega_{k2}+\mu_{k2}}\frac{1}{\omega_{k3}+\mu_{k3}} & \frac{\omega_{k2}}{\omega_{k2}+\mu_{k2}}\frac{1}{\omega_{k3}+\mu_{k3}} & \frac{1}{\omega_{k3}+\mu_{k3}} \end{bmatrix} = \begin{bmatrix} \frac{1}{\omega_{k1}+\mu_{k1}} & 0 & 0 \\ \frac{q_{k2}}{\omega_{k2}+\mu_{k2}} & \frac{1}{\omega_{k2}+\mu_{k2}} & 0 \\ \frac{q_{k3}}{\omega_{k3}+\mu_{k3}} & \frac{q_{k3}/q_{k2}}{\omega_{k3}+\mu_{k3}} & \frac{1}{\omega_{k3}+\mu_{k3}} \end{bmatrix}$$

with

$$q_{j1} = 1, q_{j2} = \frac{\omega_{j1}}{\omega_{j1}+\mu_{j1}}, q_{j3} = \frac{\omega_{j1}}{\omega_{j1}+\mu_{j1}}\frac{\omega_{j2}}{\omega_{j2}+\mu_{j2}}. \tag{9}$$

These q_{jk} factors are the fractions of infectives in the j age group that reach stage k. $\mathbf{FV^{-1}}$ will have zeros in the rows 2, 3, 5, 6, 8, 9, etc., so the eigenvectors must also have zeros in these rows 2, 3, 5, 6, 8, 9, etc. Thus we can consider the 91x91 matrix consisting of the rows $1+3(i-1)$ and columns $1+3(j-1)$ of $\mathbf{FV^{-1}}$. This matrix $\mathbf{E}$ will have ij entries given by

$$E_{ij} = \alpha_i S_i^0 \gamma_{ij} P_{ij}\left(\frac{\xi_{j1}}{\omega_{j1}+\mu_{j1}} + \frac{\xi_{j2}q_{j2}}{\omega_{j2}+\mu_{j2}} + \frac{\xi_{j3}q_{j3}}{\omega_{j3}+\mu_{j3}}\right)/N_j^0. \tag{10}$$

The basic reproduction number $\Re_0$ is the largest eigenvalue of the matrix $\mathbf{E} = \mathbf{FV^{-1}}$ [50]. We cannot obtain an explicit form of the $\Re_0$ for our general model (1). Therefore, $\Re_0$ will be estimated numerically for a given set of parameter values for the different mixing assumptions.

4 Mixing Matrices

The goal in this study is to investigate the impact that different mixing assumptions have on disease spread. Our study makes use of four different mixing models that we call normal or realistic mixing, reduced mixing, random mixing and segregated mixing.

The force of infection λ_i is the relative rate at which susceptibles of age i acquire infection at that age. Homogeneous mixing means that contacts of a person are randomly distributed among all others in the population. One immediate implication of this assumption is that the force of infection is the same for all ages. However, mixing in a population is usually heterogeneous, so contacts are not random. For heterogeneous mixing, the forces of infection reflect the age-related changes in the degree of mixing and contact, within and among age groups, which are important factors for understanding disease spread. Furthermore, changes

in behavior can alter the contact patterns in the population, which are also key in understanding disease spread.

We use the techniques developed in Del Valle et al. [49] to estimate age-dependent transmission matrices for our model. That is, we used the population of Portland, Oregon (Figure 2) used by the simulation studies of TRANSIMS [9] and EpiSims [3, 12, 47]. We calculated the total number of contacts C_{ij} (Figures 3 & 5) generated by the population over one randomly selected day and then evaluated the average number of contacts γ_{ij} per person. We obtained γ_{ij}, by dividing the total number of contacts C_{ij} by the total population N_i in age group i [49]. For the normal, reduced and segregated mixing matrices we used the average duration of contact T_{ij} reported on the surveys used by TRANSIMS and EpiSims [49]. However, for the random mixing matrix, we used a uniform distribution between 0 and 24 hours to assign a duration to each contact. Using the probability function P_{ij} given by

$$P_{ij} = 1 - e^{-\zeta T_{ij}}, \tag{11}$$

with $\zeta = 3$, we estimated the probability of transmission for the entire population.

Finally, we used the average number of random contacts γ_{ij}, the susceptibility $\alpha_i = 1$, the infectivity $\xi_{jk} = 1$, and the probability of transmission P_{ij} matrices to estimate the adequate contact matrix β_{ij} for each mixing assumption (Figures 4 & 6). Notice that we used the values of $\alpha_i = 1$ and $\xi_{jk} = 1$ for Figures 4 and 6; however, these values will be estimated later according to the susceptibility of smallpox present in the population and the infectivity of smallpox at different infected stages. The transmission matrix is the average number of adequate contacts between a susceptible of age i with people of age j.

4.1 Normal Mixing

The transmission matrix (Figure 4) is the average number of adequate contacts between a susceptible of age i with people of age j; and was estimated using the same techniques described in Del Valle et al. [49]. The normal contact matrix is formed by two blocks of mixing generated by children/young adults and adults and a weak coupling between parents and their children. Please refer to Del Valle et al. [49] for more details on the estimation of this adequate contact matrix.

4.2 Reduced Mixing

Changes in behavior in the affected population in response to knowledge of an epidemic not only reduce the number of contacts of the entire population, but they change the mixing patterns

in the population. That is, if schools close as a preventive measure to control an epidemic, the contacts of school children will change from children of their own age to their parents or family members. Therefore, one must carefully develop mixing matrices that could represent realistic mixing patterns in the presence of behavioral changes. Currently, EpiSims does not incorporate behavioral changes in their simulations, because of the lack of data to validate these changes. Thus, for simplicity we incorporate behavioral changes by reducing the number of contacts generated in the population. That is, we multiply the contact matrix (Figure 3) by a desired factor. For our numerical simulations we reduced the number of contacts by half, that is, we multiplied Figure 3 by 0.5. While recognizing the crude introduction of behavioral changes into this model, this model will serve as the foundation for later models that include validated behavioral changes in response to an outbreak.

4.3 Random Mixing

If random mixing is used, then a potential contact is randomly selected from the entire population. This implies a larger probability of meeting people from the age groups with larger sizes. Therefore, we used a random number generator to create random contacts from the age distribution of the population of Portland (Figure 2). In order to compare the random mixing matrix with the normal contact matrix (Figure 4), we matched the total of contacts of the randomly mixing population with the total number of contacts of the normal mixing population as described in [49]. The adequate contact matrix β_{ij} (Figure 6) is consistent with the age distribution of the population. That is, there are well defined regions (given by different colors) of adequate contacts, which are due to the age distribution of the population. In general, the population is more likely to have adequate contacts with people from the age groups with larger sizes (35-45 years) than with people from the age groups with smaller sizes ($>$ 55 years), which is consistent to what one would expect for a randomly mixing population.

4.4 Segregated Mixing

Our final model of the contact selection process allows for mixing only with people of the same age. That is, each age group will have the same number of contacts but all their contacts will be with their own age group. To construct a mixing matrix consistent with this idea and with the other mixing assumptions, we lumped the total number of contacts generated by each age group by a normally mixing population (Figure 3) in the diagonal. This mixing assumption will allow us to determine the factors that are driving the spread of the epidemic. That is, whether the number of contacts are driving the epidemic or the heterogeneous mixing among

the population are driving the epidemic.

5 Parameter Estimation

The smallpox infected period is divided into three phases: exposed or incubation period, prodromal period and infectious period. The incubation period for smallpox has been reported to be from 7 to 19 days, but the most common reported range is 10-14 days with a mean of 12 days [14, 44, 46]. Thus the latent phase has a relative rate of $\omega_{i1} = 1/12$. Afterward, smallpox patients experience a prodromal phase with symptoms such as fever, malaise, prostration, headache, backache, and vomiting. This period lasts for 2 to 4 days with a mean of 3 days [7, 14]. Therefore, the prodromal relative rate is $\omega_{i2} = 1/3$. Data on previous outbreaks show that patients have very low infectivity during the prodromal phase [11, 15, 38]. Therefore, we assume that during both the exposed period and the prodromal period, individuals are non-infectious. Patients remain contagious for a period of approximately 14 to 17 days with a mean of 16 days [14, 21, 22]. Hence, we set the relative rate in the infectious phase as $\omega_{i3} = 1/16$ and the infectivity as 1. Once these patients recover, they have complete, permanent immunity.

The United States discontinued smallpox vaccinations in 1972 because the vaccine itself carries potential health risks [6]. Therefore, more than half of the US population has received the smallpox vaccine, and recent findings have shown that these individuals may still have partial protection against smallpox [2, 10]. Therefore, we assume that all individuals born after 1972 are completely susceptible to smallpox. Thus, the relative susceptibility of people between the ages of 1 and 33 is set to 1. We assume that individuals between the ages of 34 and 65 have partial immunity to smallpox and thus the relative susceptibility is set to 0.3 [10]. Furthermore, we assume that people between the ages of 66 and 80 have a relative susceptibility of 0.7, and people between the ages of 81 and 90 have a relative susceptibility of 0.9 due to their age-dependent risk of infection [10].

The relative death rate of smallpox (variola major) varies, but is reported to be about 30% among unvaccinated individuals [14, 21, 22]. The fraction in the model dying from smallpox is $\mu_{i3}/(\omega_{i3} + \mu_{i3})$, setting this equal to 0.3 yields $\mu_{ij} = 0.0268$. Smallpox deaths usually occurred eighteen days or more after symptoms began [21]. Therefore, we assume that the relative death rate for each infection stage is 0, 0 and 0.0268, respectively.

Recent estimates on the transmission of smallpox indicate that 1 infected person may infect 3-6 others [16]. Therefore, $\Re_0$ was set equal to 3 for both the normal and random mixing matrices. However, for the reduced contact matrix the number of contacts were reduced by half, resulting in $\Re_0$ equal to 1.5. Notice, that by reducing the number of contacts by half,

$\Re_0$ was also cut by half. This result gives us an estimate of how much people must reduce their contacts in order to halt an epidemic. Therefore, if the number of contacts were reduced to less than one third, there would be no epidemic because $\Re_0$ would be less than 1. For the segregated matrix, we used the normal contact matrix and lumped all the entries of each age group into the diagonal. This process will result in different values of $\Re_0$ for each age group.

6 Numerical Simulations

We used a differential equation solver designed for multi-groups SIR models with staged progression developed by Chitnis et al. [40] to examine the impact that the four mixing assumptions have on the final epidemic size and final susceptible population size for our model. All simulations assume that 1 infected individual from each age group enter the incubation phase after being successfully infected during a smallpox attack. We use the baseline parameters in Table 2 in our simulations and the synthetic population of Portland, Oregon (Figure 2) as the initial population for each age group.

Table 1 summarizes the results that the four different mixing assumptions have on the final epidemic size and final susceptible population size. The final epidemic size includes both the total number of recovered cases (shown in Figures 7, 8, 9, and 10) and the total number of people who died from the disease (not included in Figures but given by $D = N - (S + I)$) at 120, 360, and 1000 days after the introduction of smallpox into the population. One column in Table 1 identifies the basic reproduction number $\Re_0$ for each mixing assumption. The final day in Table 1 is the day on which the number of smallpox cases reach 99% of the final epidemic size, which is a measure of the length of the smallpox outbreak.

The first entry in Table 1 shows the simulations results for normal mixing. With normal mixing, we obtain a cumulative total smallpox cases of $1,321,590$ after 1000 days and a final day of 324. However, when we assume reduced mixing, resulting in a smaller number of contacts per day, the epidemic decreased to $686,530$ and the final day was extended to 841. When random mixing is used, the number of smallpox cases increases to $1,429,620$ and a final day is reduced to 280. For segregated mixing, the number of smallpox cases further decreases to $1,207,470$ and the final day is extended to 1325. The total susceptible, recovered and disease prevalence for all mixing assumptions described in Table 1 are shown in Figures 7, 8, 9, and 10.

All age groups are affected differently by the disease due to the differences in susceptibility. Figure 11 shows the cumulative numbers of recovered cases, the susceptible population and disease prevalence for age groups $i = 20, 50, 65$ and 85 for a normally mixing population. Age

groups between 1 and 33 resemble the distributions shown in Figure 11, Part **a**. Notice that since we assumed no residual immunity for these age groups, they are the most affected by the disease than the rest of the population. Age groups between 34 to 61 and 66 to 71 resemble the distributions shown in Figure 11, Part **b**, even though they had different susceptibilities. Age groups between 62 to 65 and 72 to 81 resemble the distributions shown in Figure 11, Part **c**; notice that these age groups are the least affected by the disease. Finally, age groups between 82 and 91 resemble the distributions shown in Figure 11, Part **d**.

When the mixing among the population is reduced because of the assumption of behavioral changes, the number of total cases decreases dramatically. The cumulative numbers of recovered cases, the susceptible population and the disease prevalence for some age groups are shown in Figure 12. Notice that the combination of residual immunity and behavioral changes plays a key role in halting the spread of the epidemic. In Figure 12: Part **a** resembles the distributions of age groups 1-33; Part **b** resembles the distributions of age groups 32-65; Part **c** resembles the distributions of age groups 66-80; and Part **d** resembles the distributions of age groups 81-91.

When random mixing is assumed, all age groups are affected accordingly to their assumed susceptibility (Figure 13). That is, in Figure 13: Part **a** resembles the distributions of age groups 1-33; Part **b** resembles the distributions of age groups 32-65; Part **c** resembles the distributions of age groups 66-80; and Part **d** resembles the distributions of age groups 81-91. Since for segregated mixing $\Re_0$ is different for all age groups, the epidemic curves vary drastically for all age groups (Figure 14). Age groups between 1 and 33 are still the most affected as seen with previous mixing assumptions due to their lack of residual immunity (Figure 14, Part **a**). Most age groups manage to maintain a large number of susceptible individuals at the end of the epidemic because of their present residual immunity (Figure 14, Part **b** & **d**). However, there are some groups that avoid infection due to their $\Re_0$ being less than unity, these age groups are 65, 76 and 86 (Figure 14, Part **c**).

7 Sensitivity Analyses

Although the parameter values were estimated from epidemiological data, there is still some uncertainty in their values. The sensitivity analyses in this section examine the effects of changes in the number of index cases, the initially infected age group, the residual immunity present in the population, and the infectiousness in the prodromal stage.

Index Cases: The number of initially exposed individuals has a major impact on the final epidemic size for all mixing assumptions. Since we are not including any intervention strategies, the initially exposed individuals govern the epidemic in conjunction with the reproduction

number.

Initially Infected Age Group: If instead of introducing an infected individual into each age group, we introduce an infected individual into a particular age group, this results in different epidemic curves. Random mixing is not sensitive to changes in the initially infected age group, while normal and reduced mixing are slightly sensitive to changes in the initially infected group.

Residual Immunity: Differences in the level of residual immunity present in the population influence the cumulative number of infected persons. The number of smallpox cases increases when the level of residual immunity is reduced in the population and decreases when the level of residual immunity is increased in the population. Thus the simulation results are sensitive to changes in the level of residual immunity present in the population.

Infectiousness: We determined the sensitivity to changes in the relative infectivity of the prodromal phase. Most epidemiological data suggests that infectiousness in smallpox is correlated with rash onset, so that patients in the prodromal phase are generally not considered infectious [11, 15, 38]. However, some studies have suggested that individuals are highly infectious during the prodromal phase [30, 18]. Therefore, if we set the relative infectivity of each infection stage (exposed, prodromal and infectious) to 0, .5 and 1. For all mixing assumptions, the cumulative number of smallpox cases slightly increases and the final susceptible population size slightly decreases. Thus the model is slightly sensitive to changes in the relative infectivity value of the prodromal stage.

Basic reproductive number: The basic reproductive number $\Re_0$ determines the average number of secondary cases generated by each index case. Because of the lack of interventions in our model, $\Re_0$ governs the growth of the entire epidemic. Thus, all mixing matrices are highly sensitive to the reproductive number. That is, as $\Re_0$ increases, the total number of smallpox cases increases and as $\Re_0$ decreases, the total number of smallpox cases decreases.

8 Conclusions

Contact patterns are an important part of the transmission of infectious diseases. The assumption of homogeneous mixing is often sufficient to obtain general insights. However, a better knowledge of contact patterns is necessary for a more accurate estimate of the effect of residual immunity on future disease incidence. More detailed knowledge of human contact patterns could lead to studies that shed light on the long-term evolutionary consequences of public health policies.

We used a computer simulation model to investigate the impact that different mixing assumptions have on outcomes related to epidemic spread in the presence of population het-

erogeneity. Four mixing scenarios were discussed: normal mixing, reduced mixing, random mixing and segregated mixing. Our results confirm the epidemiological picture proposed in previous works, that mixing assumptions have a great influence in the overall behavior of epidemic spreading and that residual immunity can play a key role in halting an epidemic such as smallpox.

The numerical simulations in Section 6 show that random mixing results in a greater number of new infections than non-random mixing even in the presence of residual immunity. With normal mixing, the total number cases is reduced and the final susceptible population size is greater. Furthermore, when behavioral changes are introduced, the total number of cases is further reduced and the final susceptible population size is increased. We also observed that the disease affected different age groups differently based on their assumed immunity. That is, age groups with less residual immunity are more affected than age groups with more immunity. One implication of these results is that if vaccination of smallpox becomes necessary, the smallpox vaccine should be given according to the immunity present in the population. That is, those without prior smallpox vaccination should be given the vaccine first.

We studied segregated mixing to determine some of the factors that are driving the epidemic. Our results suggest that the heterogeneous mixing patterns have a greater impact on spreading the epidemic than the number of contacts. Therefore, in the face of an epidemic, the population not only have to decrease the number of contacts, but they have to stop mixing in order to halt an epidemic. Furthermore, we found that $\Re_0$ is proportional to the average number of contacts. Therefore, we can estimate how much people have to reduce their contacts in order to stop an epidemic. That is, for an epidemic with $\Re_0$ equal to 3, the population needs to decrease their number of contacts to less than one third to stop the epidemic.

Although parameter values were estimated using data, there is still uncertainty associated with their values. We found that all the simulation results are sensitive to the number of index cases, the level of residual immunity assumed to be present in the population and the value of the reproduction number. We also found that the model is slightly sensitive to changes in the relative infectivity of the prodromal phase. Furthermore, random mixing is not sensitive to changes in the initially infected age group, while normal and reduced mixing are moderately sensitive.

One of the limitation of our model is the way we implemented behavioral changes. We reduced the number of contacts by half to take into consideration the changes in behavior that the population will undertake based on knowledge of an epidemic. However, human behavior is among the most complex systems observed. Behavioral changes will not only reduce the number of contacts but will change the structure of the contact network. The SARS epidemic

is an excellent example of the dramatic behavioral changes implemented by the population as a whole and by government officials. Behavioral changes can greatly reduce the size and length of an epidemic. However, more data is needed to understand and predict the changes in behavior that a population will undertake in the presence of disease and uncertainty.

Another limitation of our study is the lack of intervention strategies. We were interested on investigating the effects of different mixing assumptions, therefore, for simplicity we did not include intervention strategies such as isolation, quarantine and vaccination. Nevertheless, one must be aware that in the presence of a deadly disease like smallpox, many intervention strategies will take place that will further decrease the spread of the disease.

We conclude that for simulations of smallpox to be useful in guiding public health policy, they must consider the impact of heterogeneous mixing, residual immunity and behavioral changes. Residual immunity within the population as well as behavioral changes implemented in the affected population can greatly affect the final epidemic size and reduce the vaccinations needed during an outbreak. It is therefore critically important to know the level of immunity in real populations from epidemiological studies and predict how the population will respond in the presence of an epidemic. The exact structure of the contact patterns in the general population is, to a large extent, still unknown. Therefore, more research is needed to increase our understanding of the impact of human contact networks and human behavior on the spread of infectious diseases, and to assess the implications of this for the planning of public health policy.

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9 Figures and Tables

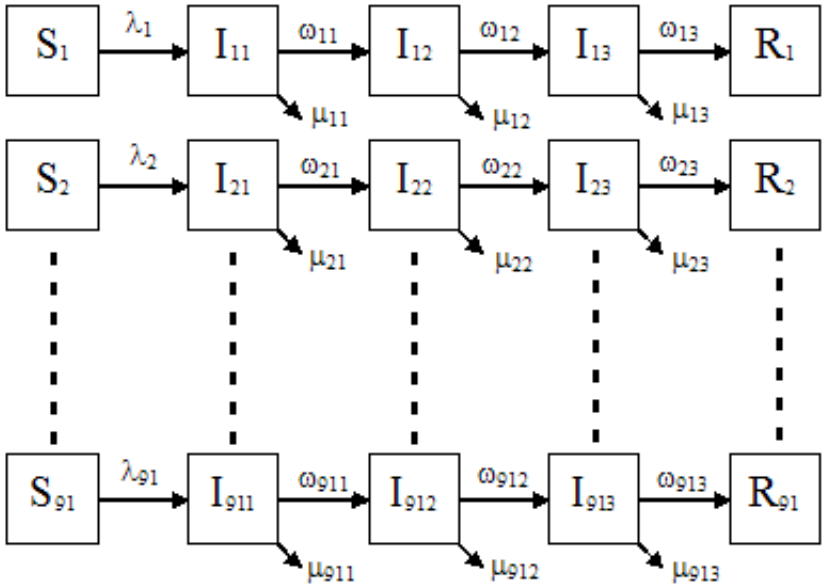

Figure 1: Schematic relationship for the multi-group SIR model with staged progression with 91 age groups and 3 infection stages. The arrows that connect the boxed groups represent movement of individuals from one group to an adjacent one. Susceptible individuals S_i get infected at a rate, λ_i, and then progress through various infection stages at rates of disease progression, ω_{ij}, before entering the recovered state. Infected individuals die from the disease at a rate, μ_{ij}.

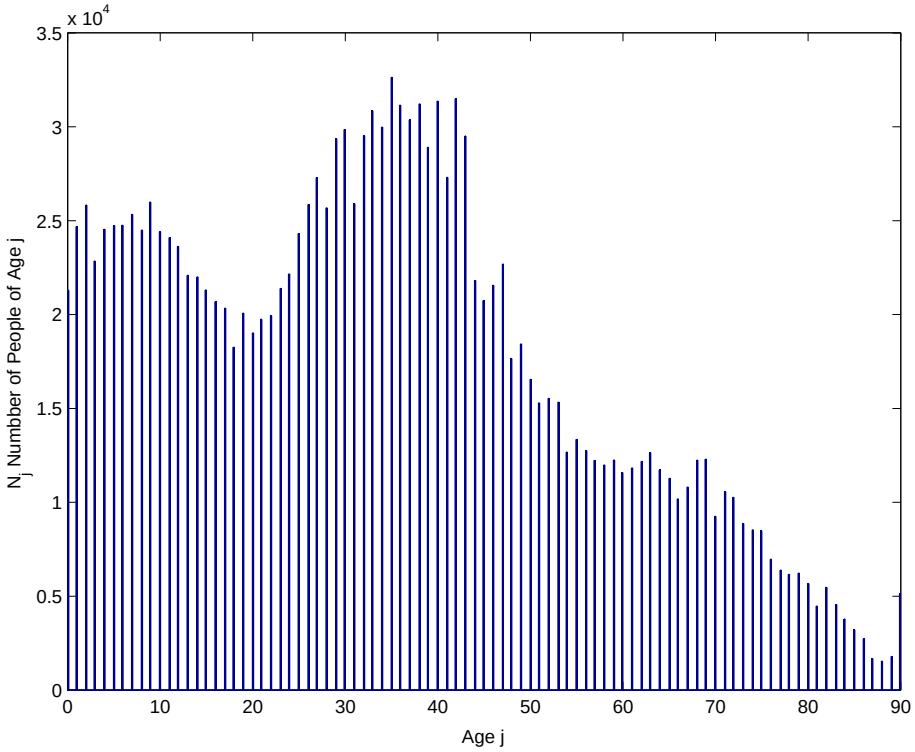

Figure 2: Age distribution of the synthetic population for the city of Portland. The population is made of 1,615,860 individuals of ages ranging from 0 to 90 years (x-axis). The y-axis illustrates the number of people in age group j, N_j. Portland is somewhat unusual because of the influx of 25-45 year old people. This results in a two-hump (bimodal) distribution with mean of 34.37 and median of 33.

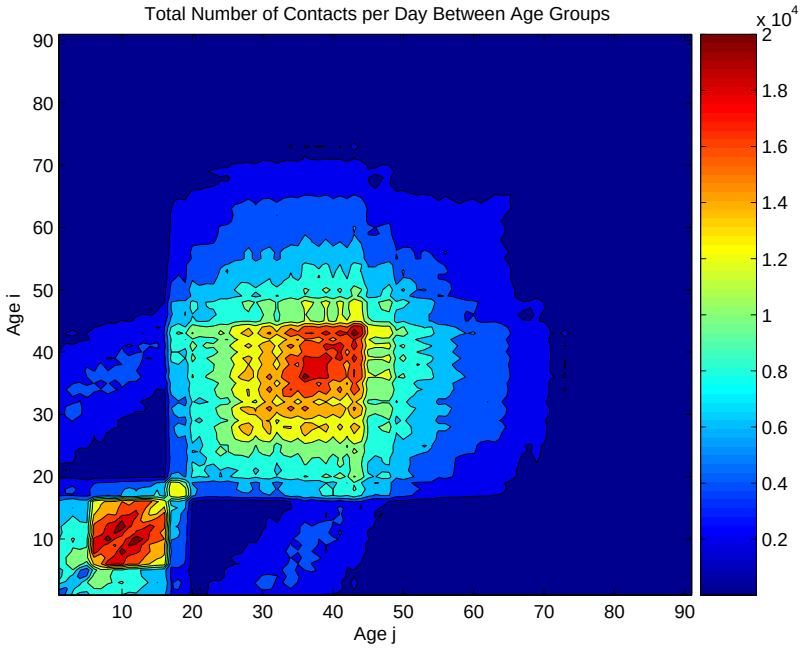

Figure 3: The total number of contacts between age groups estimated using a normally mixing population (EpiSims contact network). The contact rates are defined by the elements of the nxn matrix, C_{ij}, where C_{ij} represents the total number of contacts of all people of age i with people of age j per day.

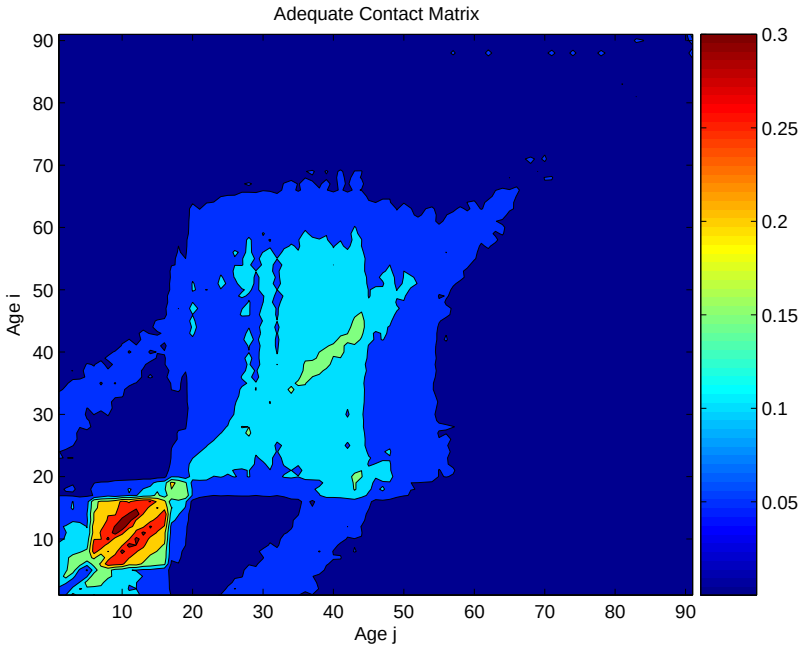

Figure 4: Transmission matrix β_{ij} estimated using a normally mixing population (EpiSims contact network). The transmission matrix is the average number of adequate contacts between a susceptible of age i with people of age j. We observe that the transmission among school children is very high compared to the rest of the population.

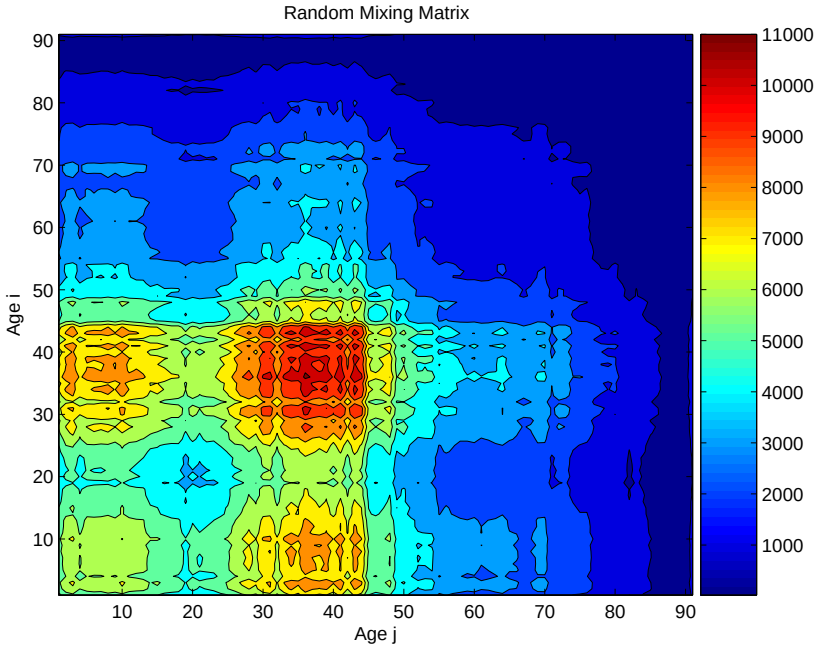

Figure 5: The total number of random contacts between age group i and j is the same as between age group j and i, resulting in a symmetric graph. The contact rates are defined by the elements of the nxn matrix, C_{ij}, where C_{ij} represents the total number of random contacts of all people of age i with people of age j per day.

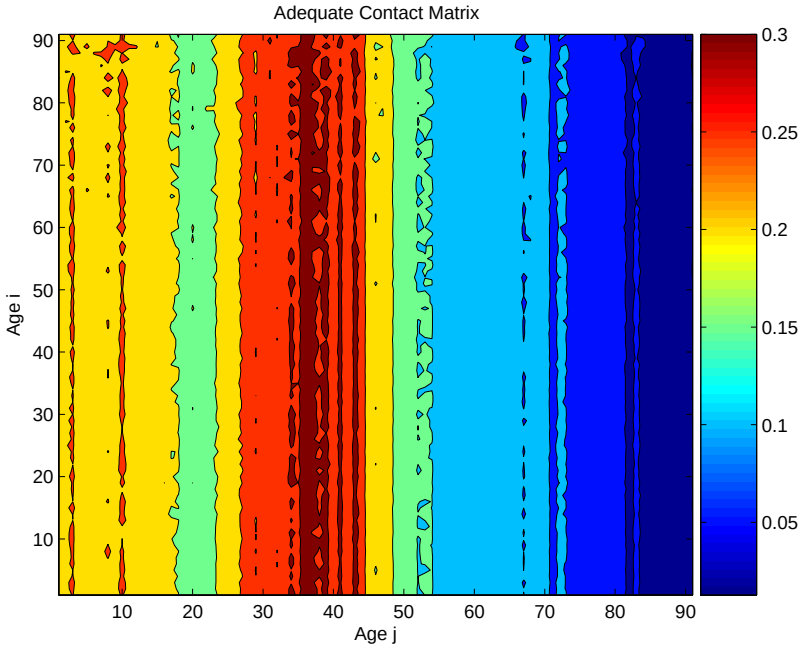

Figure 6: Transmission matrix β_{ij} estimated using a randomly mixing population. The transmission matrix is the average number of adequate contacts between a susceptible of age i with people of age j. Notice that the probability of transmission is determined by the size of the population in each age group.

Table 1: Cumulative total smallpox cases for different mixing assumptions.

Mixing Matrix	$\Re_0$	**120 days**	**360 days**	**1000 days**	**Final day**[a]
Normal Mixing	3	**33,460**	**1,317,460**	**1,321,590**	324
Final Susceptible					
Population size		*1,582,400*	*298,400*	*294,270*	*307,486*
Reduced Mixing	1.5	**1,060**	**54,460**	**686,530**	841
Final Susceptible					
Population size		*1,614,800*	*1,561,400*	*929,330*	*936,195*
Random Mixing	3	**56,760**	**1,429,100**	**1,429,620**	280
Final Susceptible					
Population size		*1,559,100*	*186,760*	*186,240*	*200,536*
Segregated Mixing		**152,960**	**786,760**	**1,207,470**	1325
Final Susceptible					
Population size		*1,462,900*	*829,100*	*408,390*	*386,349*

[a] Days from infection of index cases until outbreak is controlled (when the number of cases reaches 99% of the final epidemic size).

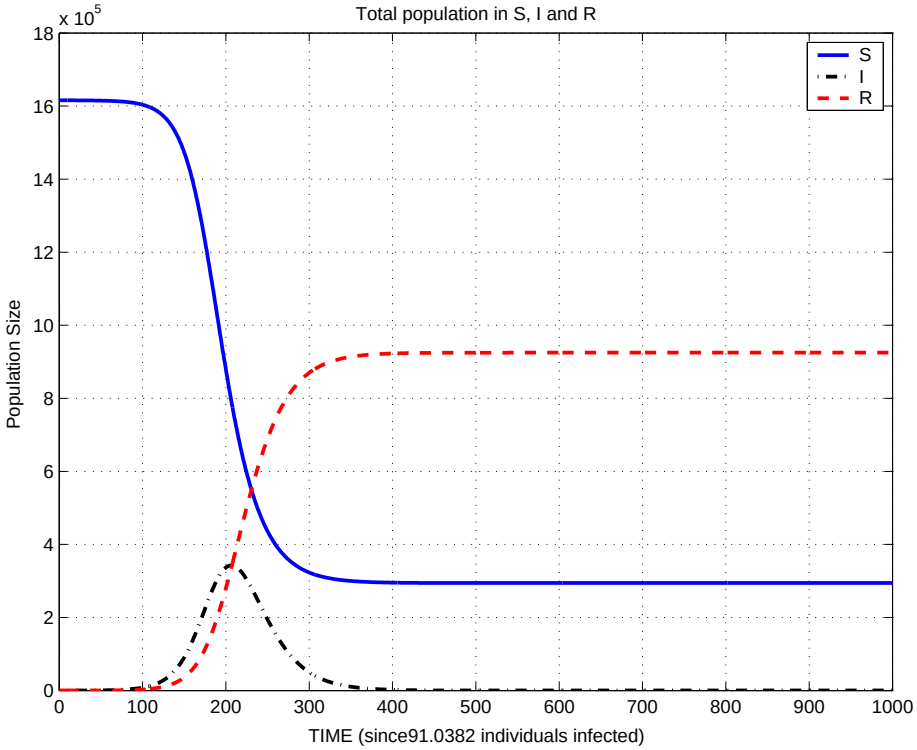

Figure 7: Solutions of the multi-group SIR model with staged progression for a normally mixing population (EpiSims mixing). The figure shows the total susceptible, infected and recovered populations for a period of 1000 days.

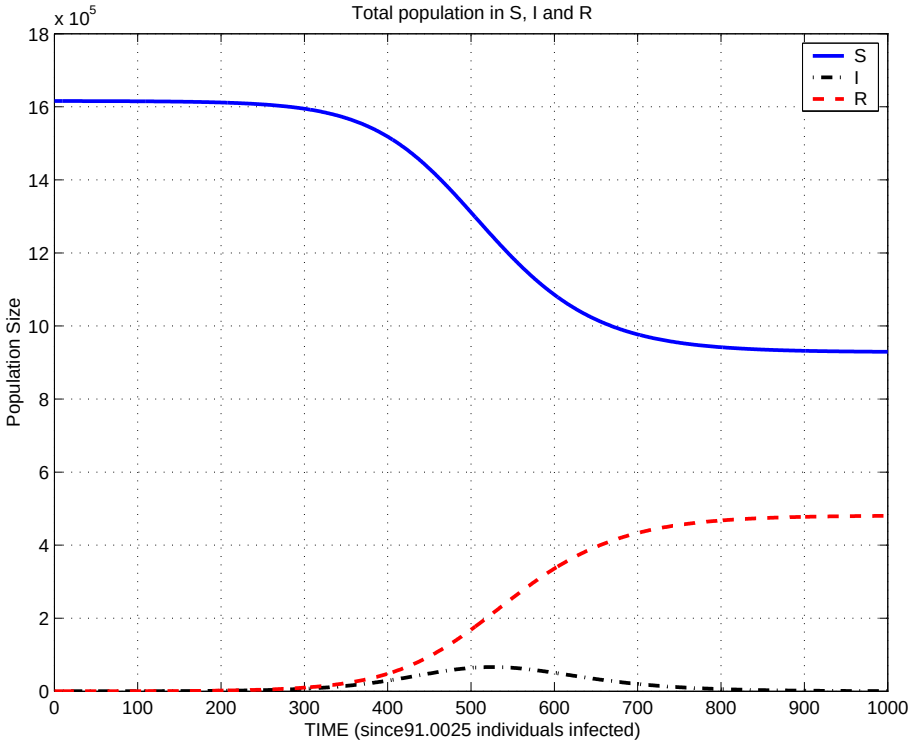

Figure 8: Solutions of the multi-group SIR model with stage progression for a population that has changed its behavior due to knowledge of a smallpox outbreak (reduced mixing). The figure shows the total susceptible, infected and recovered populations for a period of 1000 days.

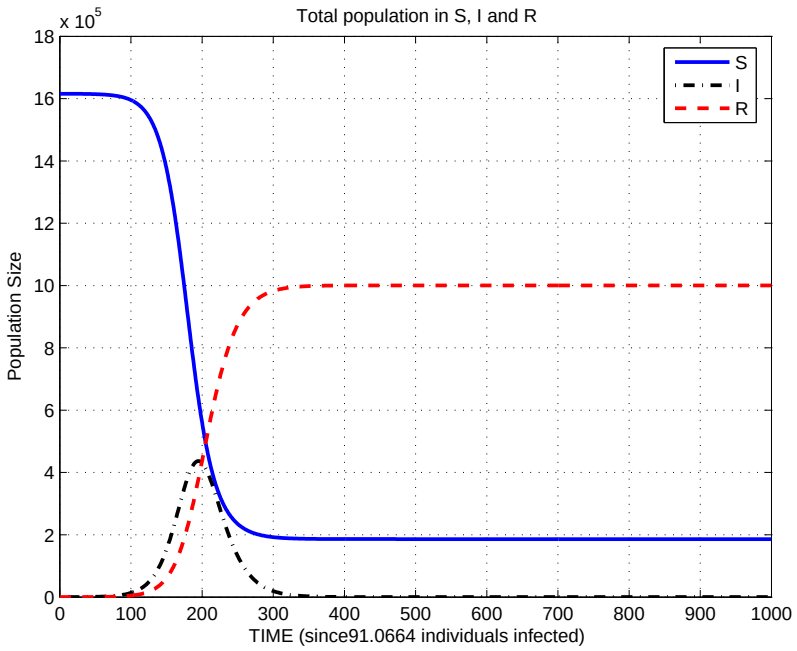

Figure 9: Solutions of the multi-group SIR model with staged progression for a randomly mixing population. The figure shows the total susceptible, infected and recovered populations of the whole system for a period of 1000 days.

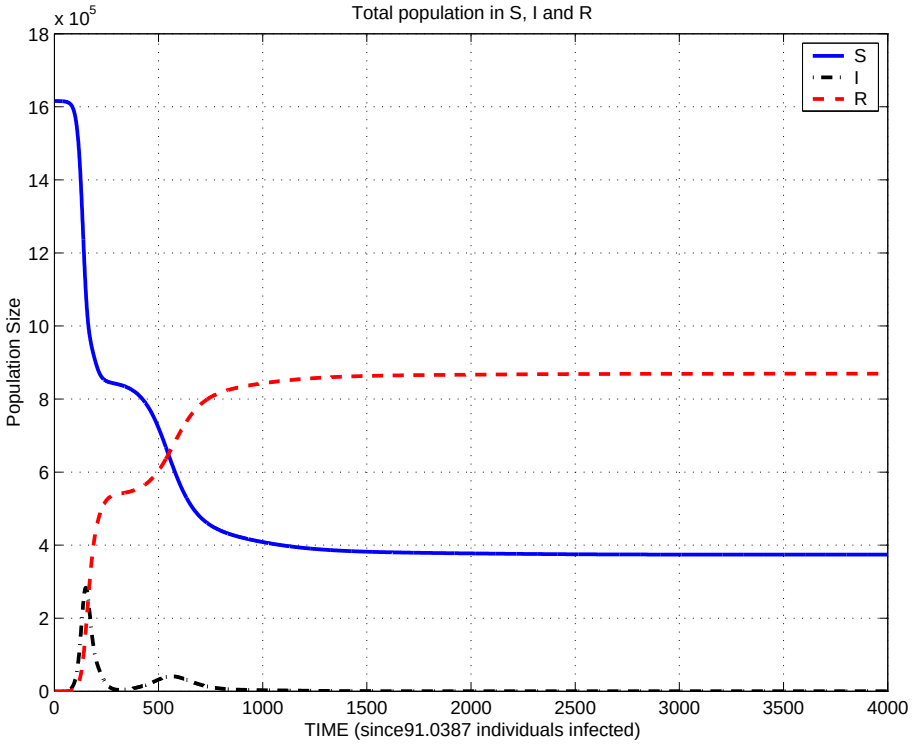

Figure 10: Solutions of the multi-group SIR model with staged progression for a segregated mixing population. The figure shows the total susceptible, infected and recovered populations of the whole system for a period of 4000 days.

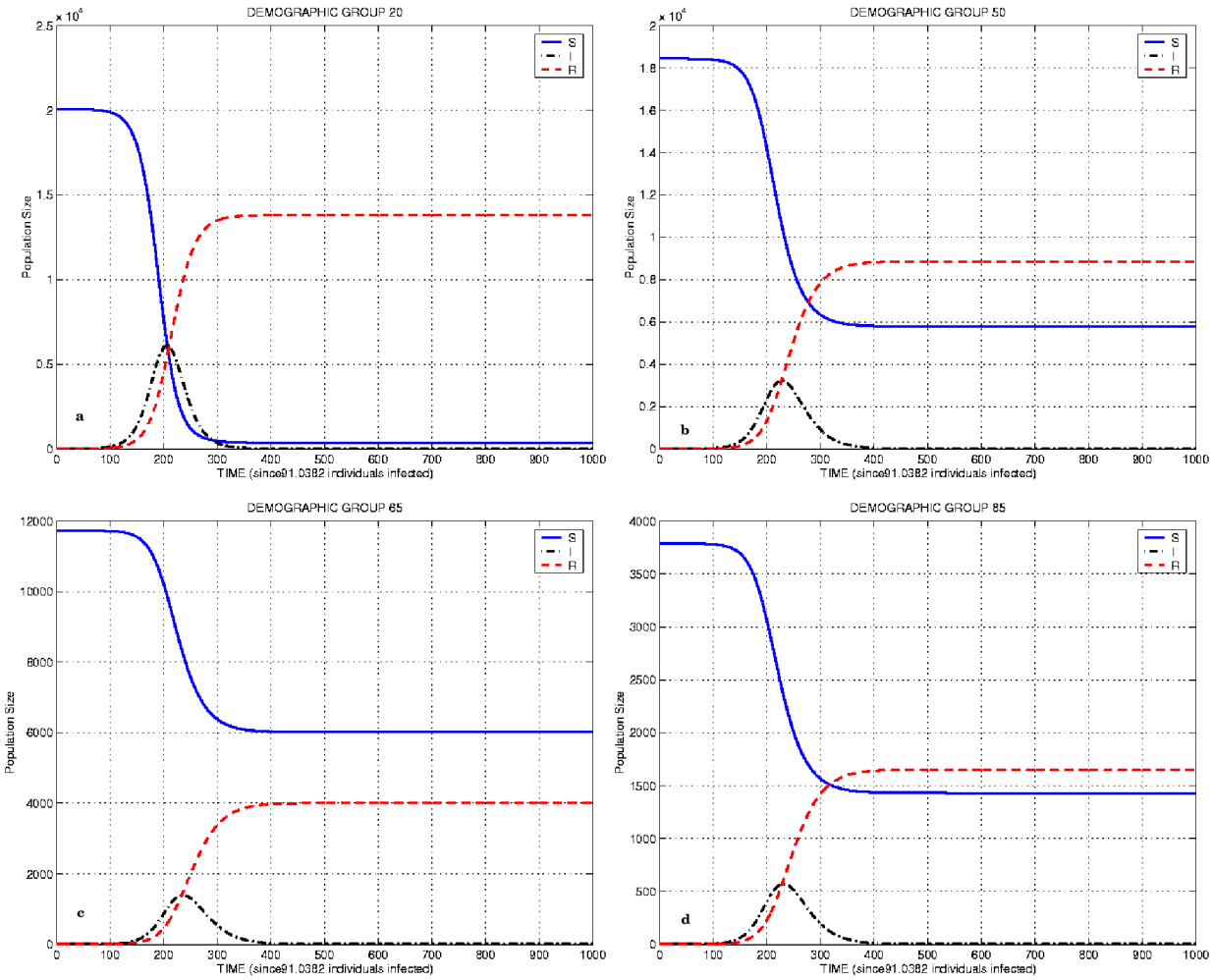

Figure 11: Solutions of the multi-group SIR model with stage progression for age groups $i = 20, 50, 65$ and 85 for a normal contact matrix. Notice the impact that partial immunity has on the final epidemic size on age groups < 34 years of age.

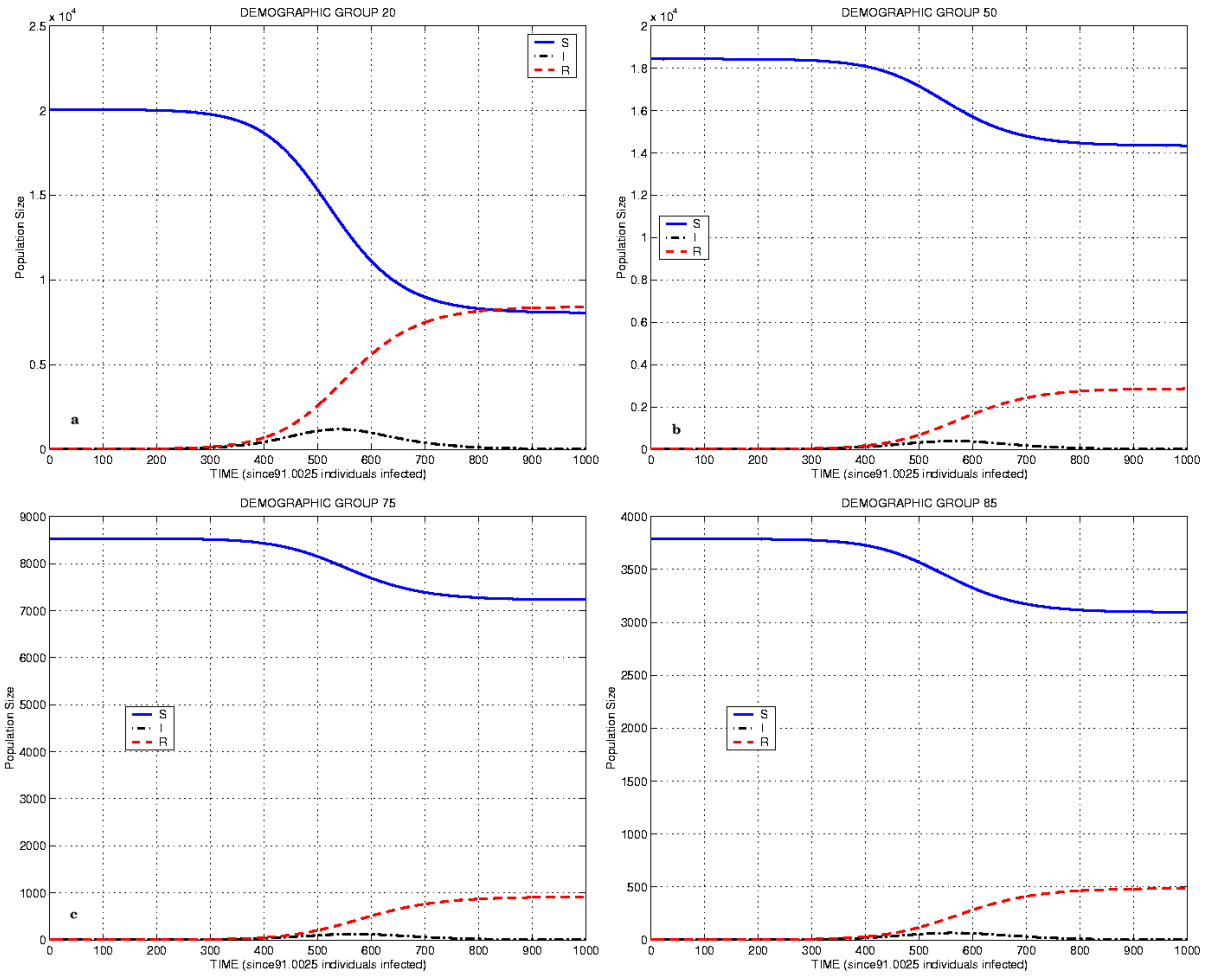

Figure 12: Solutions of the multi-group SIR model with stage progression for age groups $i = 20, 50, 75$ and 85 for a reduced contact matrix. The conjunction of residual immunity and behavioral changes have a great impact on stopping the epidemic for all age groups.

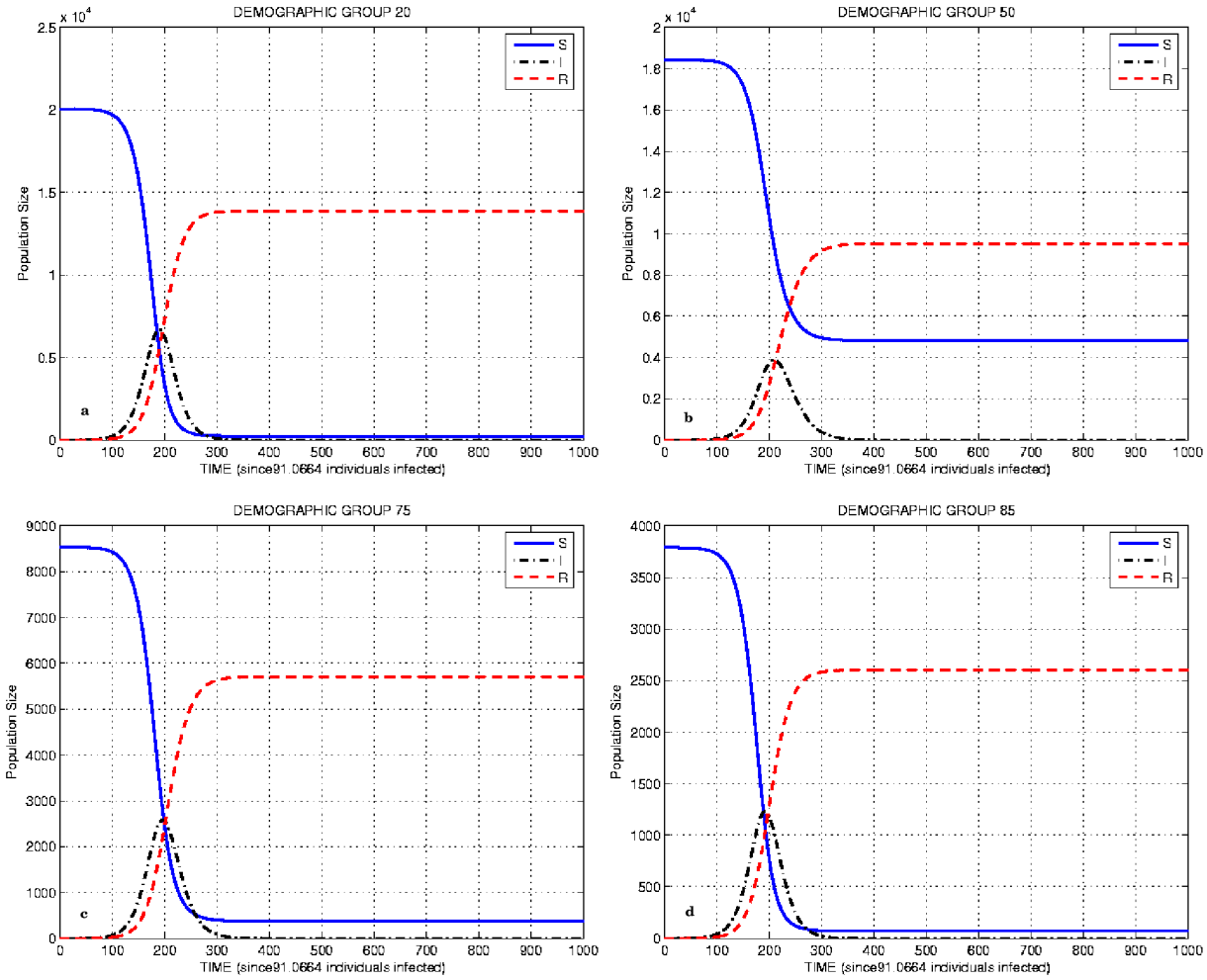

Figure 13: Solutions of the multi-group SIR model with stage progression for age groups $i = 20, 50, 75$ and 85 for a random mixing matrix. The age groups with low or no partial protection are the most affected

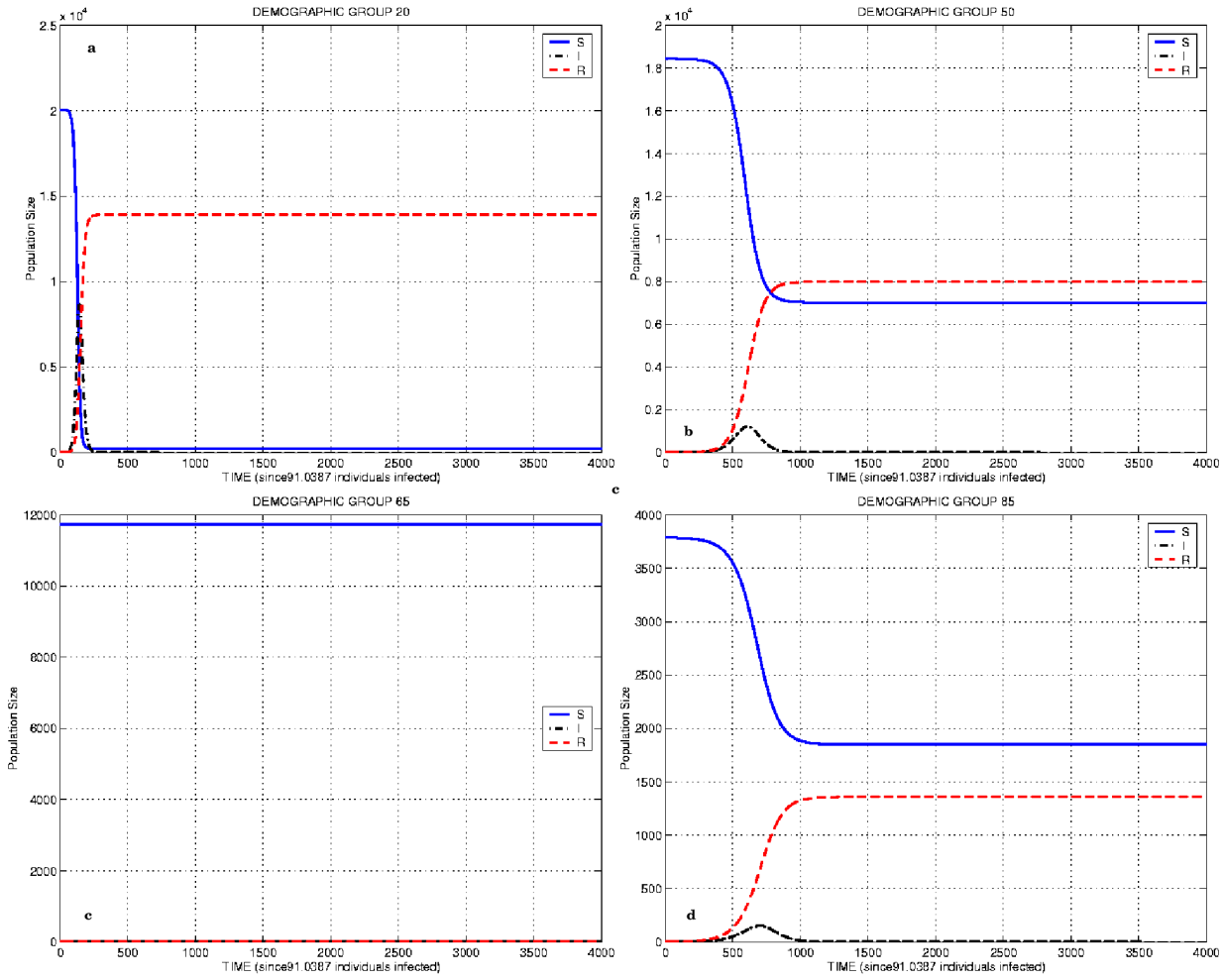

Figure 14: Solutions of the multi-group SIR model with stage progression for age groups $i = 20, 50, 65$ and 85 for a segregated contact matrix. Notice that the disease affects all groups differently due to the different values of $\Re_0$ for each age group.

Parameter	Description	Dimension	Baseline	Reference
N	Initial population size	1	1,615,860	[47]
I_{i1}	Initial infected population	1	60	See text
α_i	Susceptibility of a person in S_i for $i = 1, ..32$	1	1	[10]
α_i	Susceptibility of a person in S_i for $i = 33, ..., 65$	1	0.3	[10]
α_i	Susceptibility of a person in S_i for $i = 66, ..., 80$	1	0.7	[10]
α_i	Susceptibility of a person in S_i for $i = 81, ..., 91$	1	0.9	[10]
ξ_{ik}	Relative infectivity of each age group i	1	(0,0,0.1)	[11, 38]
ξ_{ik}	Relative infectivity of each infection stage k	1	1	See text
ω_{ik}	Relative rates of disease progression for age group i	Day^{-1}	(1/12,1/3,1/16)	[14]
ω_{ik}	Relative rates of disease progression for each stage k	1	1	See Text
μ_{ik}	Relative death rate for age group i	1	(0,0,0.0268)	[14]
μ_{ik}	Relative death rate for each stage k	1	1	See text

Table 2: Parameter definitions and values that fit the cumulative number of cases for the model.